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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,438	12/03/2001	Liming Yu	TNX95-02ABB	8540

26839 7590 01/10/2007

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EXAMINER	
CHANDRA, GYAN	
ART UNIT	PAPER NUMBER
1646	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/005,438	YU ET AL.	
	Examiner	Art Unit	
	Gyan Chandra	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-22* is/are pending in the application.

4a) Of the above claim(s) *17 and 20-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-16,18 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In view of the Appeal Brief filed on 9/22/2006, PROSECUTION IS HEREBY REOPENED. A new ground of rejection is set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing this office action.

The finality of the Office Action mailed on 11/14/2005 is withdrawn to include-include new references in view of Applicants' arguments, however a new ground of rejection is set forth below.

Claims 14-22 are pending.

Claims 17 and 20-22 are withdrawn from consideration as not directed to the elected Invention.

Claims 14-16, and 18-19 are under examination.

NOTE: Newly amended claim 14 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claim 14 recites "functional IFN-Fc variants having at least 95% identity to SEQ ID NO: 1" (line 4). The specification discloses SEQ ID NO: 1 as a nucleic acid sequence (see CRF listing), however, the claim is clearly drawn to a hybrid protein molecule.

Since applicant has received an action on the merits for the originally presented invention, claims 14-16 and 18-19 will be examined to the extent they read on an IFN-Fc hybrid protein molecule (not to an IFN-Fc variant having 95% sequence identity to the SEQ ID NO: 1).

Claim Objections

Claim 19 is objected for reciting "claims 14-18" which is inclusive of a withdrawn claim (i.e., claim 17).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 14, the claim recites "functional IFN-Fc variants having at least 95% identity to SEQ ID NO: 1" that renders the claim indefinite because the specification discloses SEQ ID NO: 1 as a nucleic acid sequence (see CRF listing). Therefore, the metes and bounds of the claim cannot be determined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14 and 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Landolfi (IDS, U.S. Patent 5, 349,053) and Frincke (IDS, EP 467416) in further view of Blatt (US Patent No. 5,373 808, 12/13/1994).

Claims 14 and 19 are drawn to an IFN-Fc hybrid molecule comprising an interferon molecule joined at one end to one chain of an immunoglobulin Fc fragment without any linker between the interferon and the immunoglobulin Fc fragment (claim 14), and a composition comprising the hybrid for treating tumors (claim 19). Claim 18 is drawn to the interferon molecule of Claim 14 wherein the interferon molecule is interferon-α2a or interferon-α2b.

Landolfi teaches making chimeric molecules that comprises a portion of a ligand molecule linked to the constant region of an immunoglobulin molecule (column 4, lines10-13) wherein the Fc region is a human gamma heavy chain (column 6, lines 51-59). Landolfi teaches,"virtually any naturally occurring ligand, including lymphokines or a portion thereof could be used to make a hybrid with Fc region of an immunoglobulin

(col.4, lines 56-60)". Landolfi teaches that immunoligands (hybrid molecules) have a number of advantages over native ligands and that short serum half-life of many ligands can be increased. It is well known in the art that within a polypeptide comprising two or more amino acids, each amino acid is linked to other amino acids through a peptide bond (-CO-NH-). Landolfi teaches that a ligand component of a hybrid protein can be conjugated to one end of an immunoglobulin component by a number of methods, for example via peptide bond by linking DNA segments encoding the ligand and the immunoglobulin constant region (col. 6, lines 44-50, and claim 5). Thus, the hybrid immunoligand protein is achieved without any linker in between a ligand and the immunoglobulin Fc fragment.

Although Landolfi contemplates using lymphokine, the group of genes which is well known to one of skill in the art to which interferon alpha belongs to, Landolfi does not explicitly teach using interferon alpha or variants thereof as a ligand. Landolfi also does not explicitly teach a composition comprising IFN-Fc or variants thereof for treating tumors.

Frincke et al teach (page 4, column 6) the administration of a complex between alpha-interferon and anti-interferon antibody (IFG 252). Frincke et al teach the term "interferon" to be inclusive of various interferons, such as interferon alpha, beta and gamma (col. 4, lines 30 and lines 37-50). Frincke et al teach that alpha-interferon has been used for treating tumors including breast cancer, multiple myeloma and malignant lymphoma (col.4, lines53-57). Frincke et al teach that when an interferon and anti-interferon antibody complex is administered in the subject, the half-life of the interferon

increased to more than twelve times as compared to the administration of interferon without any anti-interferon antibody (col. 6, lines 52-57).

Blatt et al teach that which is well-known in the art of pharmaceutical compositions comprising variants of alpha-interferon. That is, interferon-α2a and interferon-α2b have been approved for treating various tumors and that the interferon-α2a differs from the interferon-α2b by a single amino acid (col. 2, lines 10-23).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include interferon-*α* (a species of the generic ligand of lymphokines) because Landolfi teaches that virtually any naturally-occurring ligand, or portion thereof, capable of binding to a receptor may be used as the ligand, including growth factors, lymphokines, peptide hormones, lectins, and adhesion molecules (column 4, lines 56+). Further, one would have been motivated to do so because Landolfi teaches that their immunoligands have a number of advantages over native ligand molecules and immunoglobulins (column 5, lines 17+). For example, a whole new range of cells can be targeted easily because the ligand component (i.e, interferon-*α*), not the immunoglobulin, determines specificity. Additionally, the short serum half-life of many ligands can be increased by linking them to an immunoglobulin constant region. Additionally, it would have been obvious to one of ordinary skill in the art to include variants of interferon-*α*, such as interferon-*α*2a or interferon-*α*2b, because such variants were already approved in the United States (Blatt et al, column 2). Further, one would have a reasonable expectation of success in making the IFN-Fc hybrid molecule

because, according to Landolfi, these hybrid molecules can be conjugated to the immunoglobulin component by a number of methods (column 6, line 44).

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Frincke et al and Landolfi in view of Blatt as applied to claims 14 and 18-19 above, and further in view of Capon et al (US Patent No. 5,116,964).

Claim 15 is further drawn to an IFN-Fc hybrid molecule wherein the interferon is joined at its C-terminal end to the N-terminal end of the immunoglobulin Fc fragment.

The teachings of Landolfi, Frincke et al or Blatt are summarized as set forth supra. Frincke et al teach making a hybrid of IL-2 with in immunoglobulin fragment Fc, wherein C-terminus of IL-2 is joined to the N-terminus of immunoglobulin (col. 11, see vector construction). However neither Landolfi nor Frincke explicitly teaches an IFN-Fc hybrid molecule wherein the interferon is joined at its C-terminal end to the N-terminal end of the immunoglobulin Fc fragment.

Capon et al teach a fusion of a lymphocyte cell surface glycoprotein (LHR) to Fc region of an immunoglobulin. They teach that the C-terminal end of a ligand is fused to the N-terminus of the constant region of an immunoglobulin in place of variable regions thereof (col. 10, lines1-4 and claim 4).

It would have been prima facie obvious to one of ordinary skill in the art to use alpha interferon of Landolfi to fuse the C-terminal end of the interferon alpha to the N-terminus of the constant region of Fc fragment of an immunoglobulin as taught by

Capon. One of ordinary skill of the art would have been motivated to make a hybrid IFN-Fc by fusing the C-terminal end of an interferon alpha to the N-terminal end of Fc fragment as it is a preferred way of making hybrid proteins as taught by Capon et al., and there would be a reasonable expectation of success, since the chimeric proteins have been widely and successfully used in the field protein chemistry and molecular biology.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Landolfi and Frincke et al in view of Blatt et al as applied to claim 14 and 18-19 above, and further in view of Freeman et al (US Patent No. 6,130,316).

Claim 16 is further drawn to an IFN-Fc hybrid molecule wherein the Fc fragment is a gamma-4 chain Fc fragment, and wherein said Fc fragment does not induce ADCC or activate complement.

The teachings of Landolfi, Frincke et al or Blatt are summarized as above. Further, Landolfi teaches that one of skill in the art would be able to modify immunoglobulin Fc so that an effector function is eliminated or reduced.

Landolfi or Frincke et al do not explicitly teach making an IFN-Fc hybrid using a gamma-4 Fc fragment to make the IFN-Fc hybrid molecule.

Freeman et al teach a fusion polypeptide comprising an extracellular domain portion of the B7-2 protein joined to hinge, CH2 and CH3 region (which is Fc domain) of Cγ4 (col. 4, lines 66-67 though col. 5, lines 1-5 and claims 67-68). They teach that gamma-4 chain of Fc could result in an increased stability (col. 12, lines64-66).

It would have been prima facie obvious to one of ordinary skill in the art to use gamma-4 chain Fc fragment as taught by Freeman et al to make the fusion at C-terminus of alpha interferons as taught by Landolfi in view of Frincke et al. One of ordinary skill of the art would have been motivated to make a hybrid IFN-Fc using gamma-4 chain Fc fragment to provide stability to the complex as taught by Freeman et al., and there would be a reasonable expectation of success, since the chimeric proteins have been widely and successfully used in the field protein chemistry and molecular biology.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gyan Chandra whose telephone number is (571) 272-2922. The examiner can normally be reached on 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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18 December 2006
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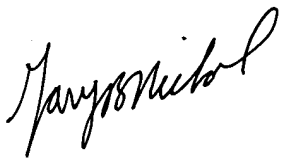

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